Communications Working Groups Meeting

HIV Prevention and MPT Product Pipeline Update

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April 3, 2013
Part 1: New ARV and HIV Prevention Products and Strategies
## Oral PrEP Study Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Product</th>
<th>Population</th>
<th>Efficacy Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPREX</td>
<td>Truvada, daily</td>
<td>MSM</td>
<td>44%, (p=0.005) 95% CI 15-63%</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>Truvada, daily</td>
<td>Serodiscordant Couples</td>
<td>62%, (p=0.0003) 95% CI 34-78%</td>
</tr>
<tr>
<td></td>
<td>TDF, 300 mg daily</td>
<td></td>
<td>73%, (p&lt;0.0001) 95% CI 49-85%</td>
</tr>
<tr>
<td>TDF2</td>
<td>Truvada, daily</td>
<td>HIV- women and men</td>
<td>63%, (p=0.013) 95% CI 22-83%</td>
</tr>
<tr>
<td>FEM PrEP</td>
<td>Truvada, daily</td>
<td>HIV- women</td>
<td>No Effect</td>
</tr>
<tr>
<td></td>
<td>TDF, 300 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VOICE</td>
<td>Truvada, daily</td>
<td>HIV- women</td>
<td>Early Termination</td>
</tr>
<tr>
<td></td>
<td>TDF, 300 mg daily</td>
<td></td>
<td>Early Termination</td>
</tr>
</tbody>
</table>
HPTN 069

PHASE II RANDOMIZED, DOUBLE-BLIND, STUDY OF SAFETY AND TOLERABILITY OF MARAVIROC, MARAVIROC + EMTRICITABINE, MARAVIROC + TENOFOVIR OR TENOFOVIR + EMTRICITABINE FOR PREEXPOSURE PROPHYLAXIS TO PREVENT HIV TRANSMISSION IN AT-RISK MEN WHO HAVE SEX WITH MEN AND IN AT-RISK WOMEN

NEXT-PREP: NOVEL EXPLORATION OF THERAPEUTICS FOR PREP

4 Arms:

- MVC 300 mg + FTC placebo + TDF Placebo each daily
- MVC 300 mg + FTC 200 mg + TDF Placebo each daily
- MVC + FTC Placebo + TDF 300 mg each daily
- MVC placebo + FTC 200 mg + TDF 300 mg each daily

**Population:** 400 men, 200 women: uninfected, at-risk, 48 wks product use

**1º Objective:** Safety- grade 3 or higher AEs

**2º Objectives:** Safety; blood compartment PK; tissue drug levels; DDI; acceptability; sexual behaviors; quality of life
## Topical ARV PrEP Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Product</th>
<th>Population</th>
<th>Efficacy Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRISA 004</td>
<td>1% TFV gel, BAT 24</td>
<td>HIV- women</td>
<td>39%, p=0.017 95% CI 6-69%</td>
</tr>
<tr>
<td>FACTS 001</td>
<td>1% TFV Gel BAT 24</td>
<td>2900 HIV- women (1:1), 18-40 yrs</td>
<td>2015</td>
</tr>
<tr>
<td>ASPIRE</td>
<td>Dapivirine IVR 25 mg</td>
<td>3476 HIV- women (1:1)18-45 yrs</td>
<td>2015</td>
</tr>
<tr>
<td>The Ring Study</td>
<td>Dapivirine IVR 25 mg</td>
<td>1650 HIV- women (2:1) 18-45 yrs</td>
<td>2015</td>
</tr>
</tbody>
</table>
MTN 013: Phase 1 safety and pharmacokinetics of dapivirine/maraviroc vaginal ring

• First combination ARV topical prevention product; first entry blocker
• Silicone matrix ring configuration
• 4 arms, 12 women per arm:
  – Dapivirine only, maraviroc only, dapivirine-maraviroc combination, placebo
• 28 day use
• Endpoints: Safety, pharmacokinetics, tissue compartment drug levels
• Pharmacodynamics assessment via ex vivo challenge of day 28 post dosing biopsies
• Follow up complete; final data analysis ongoing
Other ARV Vaginal Rings in Development

- **Maraviroc and CMPD 167 silicone matrix IVRs**
  - Malcolm et al 2012
  - In vitro characterization and macaque safety/release

- **MC1220 (NNRTI) silicone matrix IVR**
  - Fetherston et al 2013
  - Macaque safety, release and efficacy

- **MIV-150 (NNRTI) silicone matrix IVR**
  - Singer et al 2012
  - In vitro; macaque release and efficacy

- **MIV-160 (NNRTI) EVA matrix IVR**
  - Aravantinou et al., 2012
  - In vitro; macaque release and efficacy
Other ARV Vaginal Rings in Development

• Tenofovir 90 day polyurethane IVR
  – Johnson et al 2012
  – In vitro characterization and sheep safety/release

• Tenofovir “POD” IVR
  – Moss et al 2012
  – In vitro evaluation and macaque safety and compartment delivery

• Tenofovir + IQP-0528 polyurethane matrix IVR
  – Malcolm et al 2012

• TDF polyurethane reservoir IVR
  – Smith et al 2013
  – Macaque safety and efficacy
Microbicide Film Formulations

• Multiple ARV being evaluated in early stage development as vaginal films
  – Dapivirine, tenofovir, maraviroc, IQP-0528, RC-101

• Phase 1 clinical evaluation of dapivirine film vs dapivirine gel: Ongoing
  – 4 arms (2.5 gm o.5% dapivirine gel, gel placebo, 1.25 mg dapivirine film, film placebo); 15 HIV-women per arm
  – 7 days of product use
  – Grade 2 AEs or higher
  – Systemic and local absorption of dapivirine
  – Biopsy challenge PD assessment

• Combination films and scale up manufacture under investigation
Rectal Microbicides

- Primary Driver: CHARM IPCP program at MWRI (I. McGowan, PI); MTN
- MTN 006: vaginal TNF formulation
- MTN 007: Reduced glycerol TNF gel
- MTN 017: Phase II Safety and Acceptability Study of Tenofovir Gel Reformulated for Rectal Use (pending)
  - Alternating use periods of 1% TNF reduced glycerol gel and oral Truvada in HIV- men

- Other rectal microbicide work
  - New Drugs (maraviroc, Griffithsin)
  - Combination drug formulations
Long Acting Injectables:

**TMC278 (Rilpivirine):**
- NNRTI developed by Tibotec (Janssen) for treatment of HIV infection
  - 25 mg oral tablet (Edurant™) approved in US, EU, Canada
- Highly potent: $EC_{50} < 0.4 \text{ ng/mL}$ 1° HIV isolates
- Long acting nanosuspension administered IM
- 300 mg/mL packaged in glass vials
- Stable at 2-8°C for at least 24 months
- **Protect in multiple compartments of exposure**
  - Men and women
- **Adherence potential of LA formulation**
  - Higher efficacy potential
TMC278 Long Acting Injectable: SSAT 040 Phase 1 Trial

• **Study Design:**
  – HIV negative volunteers, 18-50 yrs, low risk for HIV infection
  – Single IM dose
    • 20 women per arm at 300 mg, 600 mg, or 1200 mg
    • 6 men at 600 mg

– 1º Objectives:
  • Plasma PK through day 84 post dose
  • PK in genital tract and rectal fluids/tissues

– 2º Objectives:
  • Safety/tolerability of the 4 different single IM doses of G001

– Study complete: final data analysis ongoing
TMC278 Long Acting Injectable: SSAT 040 Phase 1 Trial PK Results

Trial Summary to Date

<table>
<thead>
<tr>
<th>Matrix (D 28)</th>
<th>300 mg</th>
<th>600 mg</th>
<th>1200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>18 ng/mL</td>
<td>54 ng/mL</td>
<td>86 ng/mL</td>
</tr>
<tr>
<td>Vaginal Tissue</td>
<td>19 ng/mL</td>
<td>60 ng/mL</td>
<td>61 ng/mL</td>
</tr>
<tr>
<td>CVF</td>
<td>29 ng/mL</td>
<td>62 ng/mL</td>
<td>121 ng/mL</td>
</tr>
</tbody>
</table>

- **Male results (Day 14):**
  - Plasma = 98 ng/mL; Rectal Fluid = 23 ng/mL; Rectal Tissue = 87 ng/mL

- **TMC278 levels are 60-400 fold above EC$_{50}$**
  - Day 28 VT:plasma ratio with 600 mg SD predicts day 84 tissue levels at ~15-20 ng/mL (50 fold above EC$_{50}$)

Jackson et al, CROI, 2012
Long Acting Injectables:

**S/GSK ‘744**
- Integrase inhibitor developed via joint venture between GSK/Shionogi/ViiV
- Evaluated clinically as an oral formulation
  - Generally safe and well tolerated
  - 30 mg/d, 10 days = 2.6 log median reduction in viral load
- Well developed LAP formulation (200 mg/mL) in development for treatment and prevention indications
**S/GSK ‘744 Long Acting Injectable: Phase 1 PK and Safety**

- **Study Design:**
  - 25 women and 31 men in double blind, placebo controlled dose escalation study
  - 7 active arms, one placebo arm
    - 100 mg, 200 mg, 400 mg, 800 mg (2x400 mg) IM
    - 100 mg, 200 mg, 400 mg (2x200 mg) SC
- Safety: Generally well tolerated with mild-moderate self limited ISR as most common AE. Good systemic safety
  - No drug related grade 3-4 AEs or SAE
- **Plasma results:**
  - Prolonged $t_{1/2}$ (21-50 d) relative to oral (30-40 hrs)
  - AUC increase was roughly dose proportional
  - 800 mg IM gave exposure comparable to 30 mg daily oral
    - >20 fold above IC90

Spree et al, IAS, 2012
S/GSK ‘744 Long Acting Injectable: Macaque Efficacy Study

**Study Design:**
- 8 male macaques received 50 mg/kg at 2 time points 4 weeks apart starting 1 week prior to first virus exposure
- 8 male placebo macaques
- Intercutaneous challenge with 50 TCID 50 SHIV162p3 weekly for up to 8 exposures

**Results:**
- All 8 placebo macaques infected (mean 2 exposures)
- S/GSK ‘744 treated- no infections at 3 weeks post last challenge (final testing at 10 weeks)
- Plasma levels comparable to clinical exposure in humans

Andrews et al., CROI 2013
Part 1: Summary
New ARV and HIV Prevention Products and Strategies

• New ARV options beyond TNF and dapivirine
  – CCR5 blocker (maraviroc)
  – Integrase inhibition (S/GSK ‘744)
  – Other RTI (rilpivirine, IQP 0528, MIV-150, MIV-160, MC1220, PI)

• New IVR polymers and configurations
  – Silicone, polyurethane, EVA

• New dosage forms in the clinic
  – Vaginal films
  – Long acting injectables
Part 2: Multipurpose Prevention Technologies

- A single product, configured for at least two SRH prevention indications:
  - Contraception
  - Protection against HIV & other STIs
  - Other health benefits

Alternative configurations:

- Drug: Drug
- Drug: Device
- Vaccine
Why Multipurpose Prevention Technologies?

• Greater efficiency in terms of cost, access and delivery of SRH prevention products

• Capitalize on the demand in populations using one product type to achieve uptake and use of a second “product”
A Multitude of MPT Options

10 MPT IVR
3 On-Demand MPT
2 Barrier MPT
23 HC products

10 Single Indication IVR
12 On-Demand HIV Only
2 Injectable HIV Only
2 Lacto-based Products

31 HIV Entry Inhibitors
11 Enzyme Inhibitors
7 Other HIV Inhibitors
29 non-HC products
## Priority MPT Drugs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Priority/Comments</th>
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<tr>
<td>HIV Prevention</td>
<td><strong>Small organic molecule ARV: Potency &amp; Data</strong></td>
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<tr>
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<td>- Approved drugs over earlier stage ARV</td>
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<td></td>
<td>- Long term use safety and resistance potential</td>
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<td></td>
<td>- Focus on alternatives to RTI (e.g., TNF) <strong>GAP</strong></td>
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<td></td>
<td>- rProtein/peptides: many options; high cost &amp; risk</td>
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<td></td>
<td>- HIV drug stigma?</td>
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<tr>
<td>Pregnancy</td>
<td><strong>Hormone Based: Proven efficacy, wide use</strong></td>
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<td></td>
<td>- LNG lead (?); Others to be studied</td>
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<tr>
<td></td>
<td>- HC not prioritized for on demand use- Cycle Effects</td>
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<tr>
<td></td>
<td>- Potential risk of HIV with specific HC use  <strong>GAP</strong></td>
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<tr>
<td></td>
<td>- non HC options very early stage  <strong>GAP</strong></td>
</tr>
<tr>
<td>STI Prevention</td>
<td><strong>Alternatives to broadly neutralizing API</strong></td>
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<tr>
<td></td>
<td>- Minimal number of viable options  <strong>GAP</strong></td>
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<tr>
<td></td>
<td>- Rapid resistance selection with anti HSV drugs</td>
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</tbody>
</table>
1. Sustained Release:  
   – I.e., Vaginal Rings

2. Long Acting Injectable

3. On-Demand (pericoital)

GOAL: An MPT of each type for each of the prioritized combination indications
Priority MPT Dosage Forms: **ISSUES**

**IVR:**  
1. Multiple IVR with minor differences in development  
   a. Priority: Achieve single P3 lead  
   b. Priority: Mitigate risk of current focus on RTI  
2. Insufficient data on IVR acceptability and demand  
   a. Priority: Objectively quantify both  
   b. Address IVR w/ HC use (menses)  
3. Robustness and reliability of raw material supply chain  
4. IVR polymer compatibility with API limitations  
5. Limited number of CMO options
Priority MPT Dosage Forms: **ISSUES**

**Long Acting Injectable:**
1. Co-administration is an acceptable option
2. Equity in duration of effect required
3. Limited area of development: Additional ARV options required
4. Dosage form management:
   a. Necessity of oral run-in?
   b. Addressing long duration drug level “tail”

**On Demand:**
1. Multiple on demand formulations of same API combo not feasible
2. STI and contraception options limited (HC seen as problematic)
3. **Adherence:** Correct and consistent use? True acceptability?
4. Safety and effectiveness of intermittent ARV use
MPT Products in Development: Vaginal Rings- CONRAD, U. Utah

- Prevention of HIV & pregnancy: 90 days
- Segmented polyurethane produced via co-extrusion
- 90 day study in sheep
  - No adverse findings
  - Potentially effective levels of drug release over 90 days
- Phase 1 in Q3, 2013 (planned)
- To be resolved:
  - Storage: LNG crystal formation
  - Manufacture scale up
  - Regulatory: BE to TFV gel?

Courtesy D Friend, CONRAD
MPT Products in Development: Vaginal Rings- IPM

• Prevent HIV/pregnancy: >60 days
• Multiple prototypes in evaluation:
  – EVA core-sheath (Nuvaring)
  – Silicone matrix
  – Silicone core sheath
• Prototype selection: Aprl 2013
  – Optimization
  – Preclin evaluation
  – GMP production
• Phase 1: 2014 (planned)
• Final IVR selection with dapivirine/LNG loads: 2015

Courtesy D Friend, CONRAD
Combinations of MIV-150 (NNRTI), Zinc acetate, LNG, carrageenan in IVR or on-demand formulations

- Combination dependent prevention of HIV, HSV, HPV, pregnancy
  - Supported by animal data (HIV: macaque; HPV, HSV: mouse)
- Primary focus: Gel and IVR
- Planned clinical studies: 2016

Courtesy D Friend, CONRAD
MPT Products in Development: Barrier- Microbicide- PATH

- **SILCS diaphragm administered with microbicide gel**
  - Entering Phase 1 evaluation with TFV 1% gel in 2013
  - Developing a contraceptive TFV 1% gel in parallel

- **SILCS diaphragm that releases a microbicide**
  - Development has proven challenging

![SILCS Diaphragm side view (left) and top view (right). Image not to scale.](image)
MPT Products in Development: Long Acting Injectables

- Co-administration Strategy:
  - Rilpivirine S/GSK ‘744
  - Depo Provera
  - Cyclofem
Other MPT Product/Technology Options:

- Implants
- Lactobacillus GMO (Osel)
- Verselle Gel Delivery (FHI 360)
- Broad Spectrum Natural Products
- Proteins/Peptides
- Non-Hormonal Contraceptives
- Vaccines
Other MPT Priorities, Gaps and Comments:

**Regulatory:**
1. Engage regulators early; Familiarity at local regulatory level
2. “Bridging” dosage forms via BE studies: Potential challenges

**Social/Behavior:**
1. Critical to study MPT in adolescent populations
2. MPT needs and issues will differ regionally

**Access and Delivery:**
1. Proof of demand (not need) early in development
2. Accurate and relevant forecasting
3. Policies and practices of the procuring entity
4. Manufacturability and automation
5. Supply chain (raw materials, finished product)
6. Delivery channels (last mile!)
7. Partnering options
Thank You and Questions